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Review article

Assessing the potential of mathematical modelling in designing drug-releasing orthopaedic implants

David King, Sean McGinty *

Division of Biomedical Engineering, University of Glasgow, Glasgow, UK

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ABSTRACT

Orthopaedic implants have been the subject of intense research in recent years, with academics, clinicians and industrialists seeking to broaden our understanding of their function and potential consequences within the human body. Current research is focussed on ways to improve the integration of an orthopaedic device within the body, whether it be to encourage better osseointegration, combat possible infection or stem the foreign body response. A key emerging strategy is the controlled delivery of therapeutics from the device, which may take the form of, for example, antibiotics, analgesics, anti-inflammatories or growth factors. However, the optimal device design that gives rise to the desired controlled release has yet to be defined. There are many examples in the literature of experimental approaches which attempt to tackle this issue. However, the necessity of having to conduct multiple experiments to test different scenarios is a major drawback of this approach. So enter stage left: mathematical modelling. Using a mathematical modelling approach can provide much more than experiments in isolation. For instance, a mathematical model can help identify key drug release mechanisms and uncover the rate limiting processes; allow for the estimation of values of the parameters controlling the system; quantify the effect of the interaction with the biological environment; and aid with the design of optimisation strategies for controlled drug release. In this paper we review current experimental approaches and some relevant mathematical models and suggest the future direction of such approaches in this field.

Contents

* Corresponding author.
E-mail address: sean.mcginty@glasgow.ac.uk (S. McGinty).

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1. Introduction and background

1.1. Background

Orthopaedic implants (OIs) have proven to be a very successful addition to the field of medicine. Examples of these devices include plates, screws and intramedullary rods to stabilise fractures, prosthetic hip and knee joints, and replacement intervertebral disks. Traditionally, OIs were designed to serve one of two purposes: either to act as a fixation device to provide mechanical stabilisation or to replace a joint or bone, such as a hip replacement. The former is achieved by reducing the stress and strain on the affected bone, essentially sharing the load. The mechanical stabilisation of bones via the implant allows for optimal bone positioning which can be maintained during physiologic loading and thus the implant aids the natural healing process of bone. OIs allow for restored mobility, reduced pain and improving the overall quality of life for millions of recipients the world over [1].

OIs started as simple mechanical devices, however, complications quickly became apparent. There are many factors to consider, such as the physical impact the device has on the bone and surrounding soft tissue; the inevitable foreign body response; the possibility of post-surgical infection; whether or not osseointegration can be achieved (the successful functional and structural connection between bone and implant) and several other obstacles.

1.2. Challenges

In an attempt to overcome the many challenges facing orthopaedic device usage, many experimental research approaches have appeared in the literature, that examine the various aspects of OIs. As well as the need to ensure that OIs have the necessary mechanical properties [2–4], the materials from which they are made must be biocompatible [2,5], and many studies have been dedicated towards investigating the biocompatibility of novel OI materials [2,3]. These studies include, for example, determining possible cytotoxic effects and corrosion resistance [2–4]. It has been suggested that many of the remaining challenges (e.g. osseointegration, inflammation, infection and pain) may be tackled by the local delivery of therapeutics. Infection is one of the major causes for concern following surgery, and although care is taken to sterilise the equipment and the implant to be fitted, infections do arise [5–9].

The local delivery of drugs in orthopaedic applications is not new. Indeed, antibiotics have for years been routinely delivered locally following joint replacements such as prosthetic hips. However, the antibiotics have been contained within the cement that is used to secure the implant in place [5,8], rather than embedded within the implant itself. The result is that there is next-to-no level of control over the release: drug is typically delivered at concentrations well in excess of the minimum inhibitory concentration (MIC) of bacteria [10]. Furthermore, the high dependence on surface area and porosity of the cement makes it difficult to control and reproduce a desired release profile, especially since the drying process of the cement results in the unpredictable formation of cracks and other defects [10]. Recently, there has been a move away from OIs which require the use of cement. The main driver for this change of tack has been the introduction of OI materials which exhibit rough surfaces that provide a "snug fit", rendering the use of cement redundant. There is also a benefit for the patient in terms of a reduction in the procedure duration, due to the lack of need to wait for cement to dry. Whilst antibiotics may in principle be coated onto the rough surface of these newer implants, to the best of our knowledge, no such implants have yet made it into clinical practice. The lack of local delivery of antibiotics in these applications is a concern, and is certainly an area where research efforts should be focussed.

Experimental approaches which have investigated drug release have typically contained drug within hollowed out portions of the implant [10–12], a coating on the surface of the implant [1,5] or a modified surface/structure of the implant [13–15]. The drug may be an anti-inflammatory, such as dexamethasone, to help with the foreign body response; an antibacterial/antimicrobial agent, such as linezolid and cefazolin, to fight off/prevent infection; analgesics, such as tramadol, for pain relief; or perhaps even growth factors to encourage wound healing. Whilst the experiments that have been conducted thus far show promise for the development of drug-eluting OIs, to the best of our knowledge none of these prototypes/designs have yet made it into clinical practice. One of the issues regarding the design of drug-releasing OIs is that whilst it is clear that controlled release is required, it is not always clear what the desired release profile is. Controlled release is of great importance since if the concentration is too high a toxic effect could occur or if the concentration is too low the desired therapeutic effect could be lost. The challenge is to be able to maintain a drug concentration level that is within some therapeutic range, often for an extended period of time. Particularly in the case of antibiotics, care must be taken to ensure that drug delivery below the minimum therapeutic level is avoided, since long-term exposure is associated with antibiotic resistance [2]. In order to be able to control the release for a given OI, one must have a good understanding of the drug release mechanism(s). Experimental approaches have provided insights in this regard, but when there are a number of possible mechanisms involved, the relative importance of each is not always clear and so predicting the effects of changes in system parameters can be challenging. For example, from experiments it may appear that diffusion is the dominant release mechanism for a given drug, but if the drug is replaced with another of substantially lower solubility, then the rate of drug release may be limited by the rate of dissolution. Varying other system parameters such as the thickness or porosity of a drug releasing coating; the material the coating is made from; or the physico-chemical properties of the drug itself may result in the dominant release mechanism changing and introduce such effects as erosion, swelling, degradation and interactions between the drug and the material itself.

To the best of our knowledge, no mathematical models of OIs exist that attempt to solve the controlled release issue, which is unfortunate as mathematical modelling is capable of helping to determine the key drug release mechanisms and uncover the rate limiting processes; estimate the values of the parameters controlling the system; quantify the effect of the interaction with the biological environment; and aid in the design of optimisation strategies for controlled drug release. It is important to note that OIs were never engineered to carry and release drugs, so incorporating drugs into OIs and controlling the release is a great challenge [16].

1.3. Outline

The purpose of this paper is two-fold. Firstly, it will serve as a brief overview of experimental approaches which have attempted to aid in the design of drug-releasing OIs. Secondly, it will outline mathematical approaches that may allow for a greater understanding of how to control the release of drug from OIs, such that drug is delivered and maintained at the appropriate levels for the correct duration. This paper is not intended to present a fully comprehensive review of experimental approaches, but rather to give a feel for the existing experiments, the challenges that have been faced, the questions that have arisen and to indicate how mathematical modelling can assist in addressing these issues.

2. Experimental approaches to enhance current knowledge on drug release

The final clinical outcome is determined by the biological and mechanical characteristics of the bone healing process and so the integration of orthopaedic devices must allow this process to continue and aid it if possible. To this end, many researchers are looking at various ways to enhance current OIs or produce new ideas for orthopaedic

devices. Such approaches include experimenting with drug-filled orthopaedic implant designs [10–12], the application of a coating to the implant surface which releases drugs [1,19], altering the surface of the bare implant to act as a drug reservoir [15,18] and exploring new materials for device construction which could hold drugs [2,20]. Indeed, numerous experimental approaches have been devised to examine the combination of drug-elution with an orthopaedic device.

2.1. Drug filled orthopaedic implant designs

Focussing on local infection, Gimeno et al. [11] examined the release rates of two dry solid antibiotics (linezolid and cefazolin) from hollow stainless steel (widely used in the manufacture of OIs) medical grade tubes, where the hollowed-out portion of the tubes acted as a reservoir for each drug (Fig. 1, Image 1). This was a proof-of-concept study, with the intention being that the hollow tubes would be developed into drug-eluting fixation screws. Each tube was filled with either linezolid or cefazolin and machined to have either 2, 4, 6 or 8 equidistant orifices, through which the drug could be released into the surrounding simulated body fluid (SBF, Kokubo solution). The in vitro experiments were performed in triplicate, in stirred conditions, without the renewal of SBF. The authors demonstrated that the drug release rate could be modified by varying the number of orifices in each tube. However, they were not able to fully explain the similar release profiles of both drugs in the case where the tubes had 2 orifices, despite cefazolin having a much greater water solubility, whereas the release profiles were markedly different for 4, 6 and 8 orifices (Fig. 2).

In addition, the release profiles for linezolid were highly non-intuitive, especially for the tubes with 6 and 8 orifices. The authors also tested the infection fighting abilities of the drug-filled tubes and used the tubes with 4 and 6 orifices, along with a control which had no antibiotic. They found that both drugs were able to diffuse out of the tubes with 4 and 6 orifices into the surrounding medium and kill off the bacteria. An increasing bacterial population was found in the control experiment.

An experiment which features a two-stage antibiotic-eluting device, was conducted by Perez et al. [12], who examined the release of linezolid from hollow stainless steel medical grade tubes with porous walls (Fig. 1, Image 2). The hollowed-out sections of each tube were filled with spherical mesoporous silica microparticles loaded with linezolid. Three tubes were experimented with under stirred conditions and the resultant release profiles show an increasing concentration of the antibiotic in the surrounding SBF (which was replenished once). According to the authors, noticeable differences in the release profiles may be due to slight variations in the porosity of each tube during the manufacturing stage; small differences in the amount of drug that was loaded into the particles; or perhaps packing density [12]. Perez et al. demonstrated the bactericidal effect of these tubes, observing a 3 orders of magnitude bacterial growth reduction after 48 h. It was noted that the release profile of linezolid flattened out at a concentration that was much lower than the predicted maximum concentration, suggesting that the concentration of drug in both the SBF and the device may have reached an equilibrium. In a real-life setting, the fluid surrounding an implant would be continuously renewed and so further drug release is achievable: this was tested by renewing the media and further drug release was confirmed (Fig. 3).

It is also noted that this design offers good flexibility since it is a two-stage release device and depending on the release profile required, this could be achieved via altering the characteristics of the silica particles and the porous wall of the tube independently.

The aforementioned implant design was further tested within an ovine study by Gimeno et al. [10], although the device was instead filled with solid linezolid rather than drug-loaded particles. Their in vivo experiment was successful, as after 7 and 9 days following the addition of biofilm forming bacteria, the sheep did not show any signs of infection. This altered implant was also tested in vitro by submersing the device in SBF. The results showed that the implant released almost 75% of the antibiotic during the first four days and sustained release for at least one week. The release profile obtained from the experiment was almost linear (Fig. 4), in contrast to the

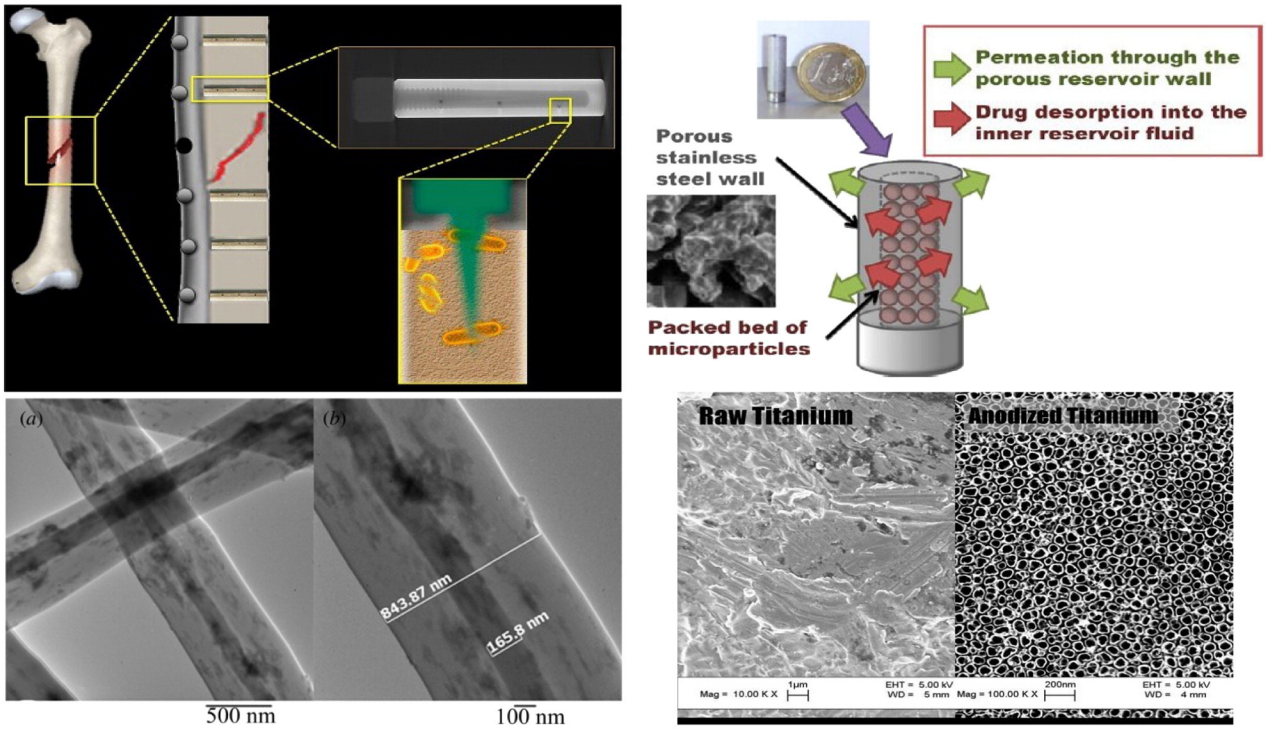


Fig. 1. A selection of experimental approaches: Image 1 (top left): prototype drug releasing tube by Gimeno et al. [11]. Image 2 (top right): a similar prototype drug releasing tube with porous walls by Perez et al. [12]. Image 3 (bottom left): a view of the nanofibres experimented with by Song et al. [17]. Image 4 (bottom right): an example of a nanotubular surface in the experiments by Aninwene et al. [18].

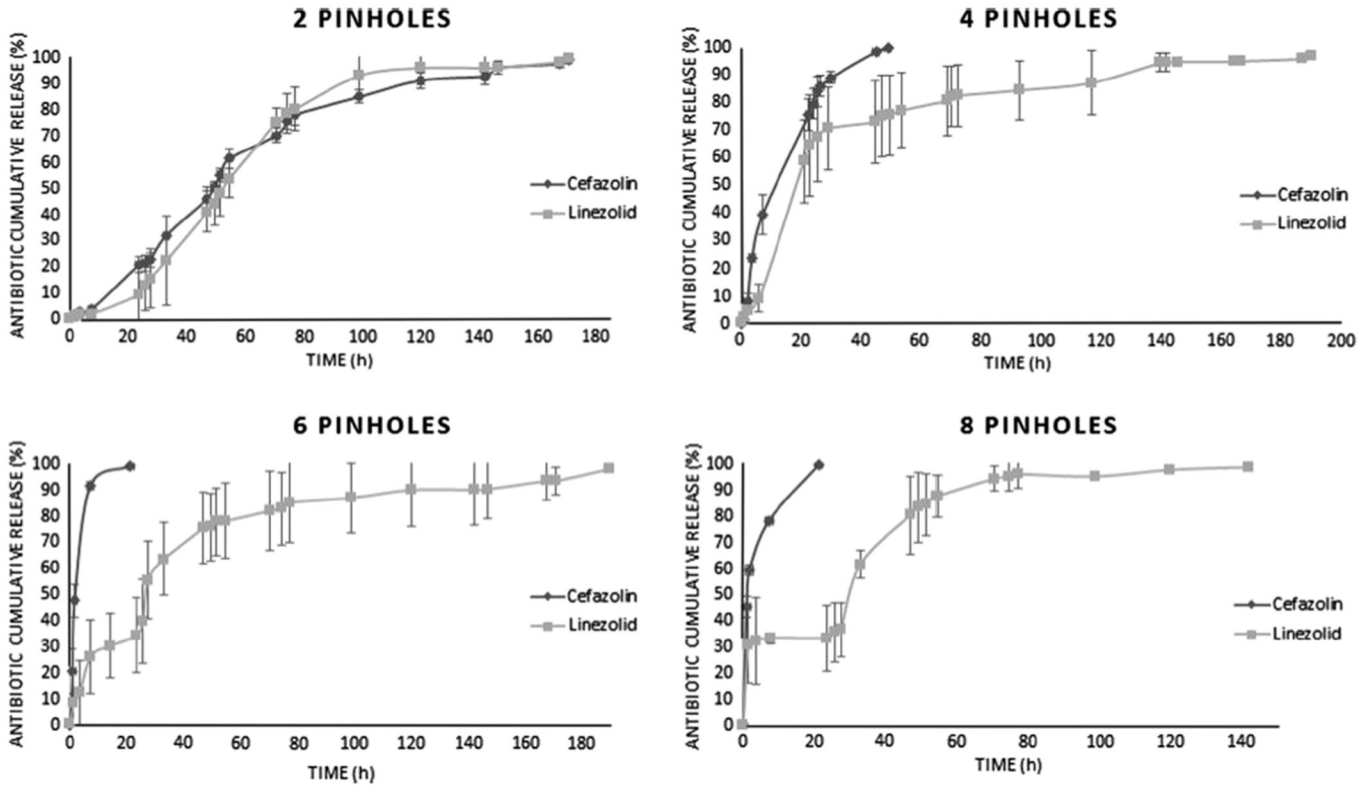


Fig. 2. Release profiles for drug-filled tubes with varied numbers of orifices (pinholes). Reproduced from [11].

bi-phasic release profile obtained in the case of mesoporous silica particles (Fig. 3).

2.2. Drug releasing coatings for orthopaedic implants

Drug releasing coatings have been given much consideration in recent years in orthopaedic applications [1,2,6,19,21]. These coatings can take several forms. For example, bone-like materials such as Hydroxyapatite have been shown to be capable of storing and releasing drugs [1,2,19], whilst exhibiting favourable biocompatibility properties. Hydroxyapatite may aid osseointegration, however, the lack of controllability of drug release has been cited as a potential issue [17]. Other coatings considered include durable/biodegradable polymers [9,22], gels [23] and nanofibers [17,24].

In an attempt to tackle the issue of post-surgical infection associated with the implantation of an orthopaedic device, Kaur et al. [22] assessed the drug-eluting and antibacterial qualities of polymer/drug coated Kirschner wires (K-wire) in vitro. K-wires were coated with a biodegradable poly-D,L-lactide (PDLLA) and linezolid mixture. PDLLA is a polymer that is used for coating other medical implants and is noted for its biocompatibility and mechanical stability [22]. Three polymer/linezolid mixtures were used (2.5%, 5% and 10% linezolid), and K-wires were dipped three times to ensure an even coat. Two drug-free wires were also used, with the first featuring a polymer-only coating, and the second had no coating at all. The K-wires were suspended in bacterial solutions containing either MRSA (Methicillin-Resistant

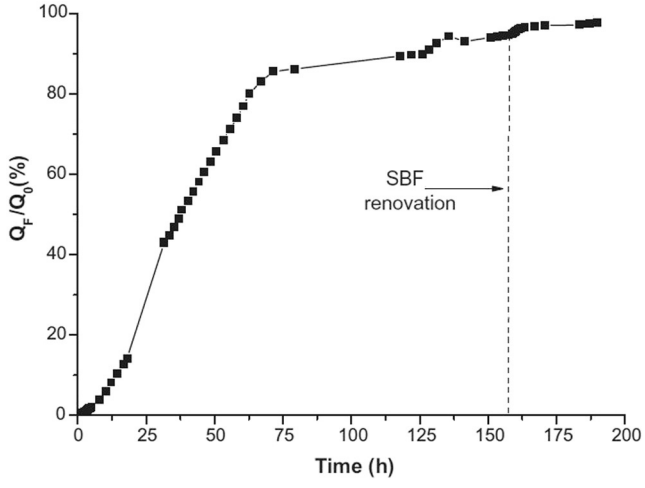


Fig. 3. Release profile from two-stage antibiotic releasing implant, indicating that drug release continued after renewing release media. Q_F/Q_0(%) represents the cumulative % of drug released. Reproduced from [12].

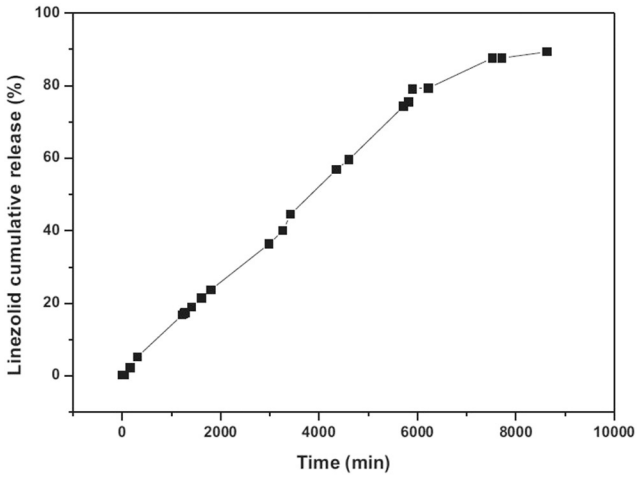


Fig. 4. Cumulative drug release from a porous hollow implant, showing an almost linear profile. Reproduced from [10].

Staphylococcus aureus) or MSSA (Methicillin-Sensitive *Staphylococcus aureus*), so that bacterial cells could adhere to the surface of the K-wires. The K-wires were placed into phosphate buffered saline (PBS) solution and during a 120 h period, samples were taken to determine the amount of linezolid released. The results of the experiment showed a linezolid concentration above the MIC for all three polymer/linezolid K-wires (Fig. 5).

The wires with the two highest concentrations were reported to exhibit sustained release of linezolid and although the linezolid concentrations sampled at 120 h was minimal, it was between 8 and 16 times higher than the MIC. In the case of the wire with the lowest concentration, there was a peak concentration at 24 h, after which, the linezolid concentration began to decrease. The results also showed a significant decrease in the number of bacterial cells adhered to the surface of the wires. The authors mention that the effectiveness of devices such as these is dependent on the release profile of the drug, as a high initial release rate and a subsequent prolonged period of drug release is required to ensure that the drug concentration is above the MIC. Although the bacteria used in the experiment were not completely eradicated, Kaur et al. note that the significant reduction in their numbers would go a long way to limit the possibility of infection post-surgery, since the immune system could handle the remaining bacteria.

Argarate et al. [9] investigated the drug-eluting qualities of poly(D,L-lactide-*co*-lactide) (PLDL) disks coated with the biodegradable polymer poly(L-lactic acid) (PLLA). The drugs used in the experiment were eugenol (EG) and dexamethasone (DM), which gave the PLDL disks both antibacterial and anti-inflammatory qualities. The PLDL disks were coated by dipping them into solutions of varying concentrations of PLLA. The authors observed that the thickness of the polymer coating could be modified via altering the concentration of PLLA in solution, with coating thickness increasing with concentration. For the in vitro drug-elution experiments, they prepared three sets of coating for the PLDL disks: 1) a direct coating of EG; 2) a layer of PLLA mixed with EG and; 3) a layer of PLLA and EG followed by a second coat of PLLA and DM. Three disks in each coating set were used in the experiments. The disks were immersed in PBS solution, in a water bath shaker. At regular time intervals, up to 8 weeks, samples of the PBS solution were taken to evaluate drug release and fresh PBS was added to replace the samples taken.

It was observed that the polymer coating was uniformly distributed on the PLDL disks and that a rough surface was obtained from the coating, which may help in osteoblast adhesion [9]. It was noted that a direct coating of EG delivered drug rapidly when compared to the single and bi-layered PLLA coats. It was shown that the bi-layered disks had a total drug delivery less than that obtained from disks with one layer of coating and it was suggested that this may be due to the relatively large diffusion distance, with a bi-layer coating, to the surrounding medium. The combined bi-layer disks of both DM and EG showed that DM was delivered quicker than EG, this was due to DM being contained within the upper layer, which resulted in a quick release during the first week, after which the release plateaued up to 8 weeks. The inner layer, containing EG, delivered almost half of the drug within 4 days, then steady release for the remaining first week was observed. After which, the release plateaued up to the 8th week of the experiment. (Fig. 6). The authors concluded that controlled sequential release of two drugs from a bi-layered coating on implants is possible.

Radin et al. [23] examined the release of vancomycin from thin sol-gel films on titanium alloy plates, a material often used in fracture fixation. Their research was inspired by the fact that sol-gel films are biocompatible and that room temperature processed silica sol-gels are nanostructured and porous materials [23], which are ideal for controlled release. The experimental setup consisted of Ti-6Al-4V (an alloy of titanium) strips which were dipped into a sol-gel solution containing differing vancomycin concentrations numerous times to apply a varying number of layers to the alloy samples. Studies of the degradation of the sol-gel films and of the release of vancomycin in PBS solution were carried out, with daily renewal of the media. Their results showed a time-dependent release of vancomycin and when the coatings were comprised of 2 or 3 layers, a significant increase in the release rate, the total amount of drug released and duration of release was found (Fig. 7).

A close connection between the degradation rates and the release rates was inferred. The authors concluded that a long-term release can be achieved by the use of multi-layered coatings and that the degradation and release rates can be tailored by varying the parameters in the process of producing the sol-gel. The findings also allude to the conclusion that coating degradation is a governing mechanism in the release of the drug. This experiment highlights the suitability of a sol-gel coating as a drug releasing method and this approach has the benefit being able to vary multiple parameters to tailor the release rates depending on the application. The possibility of applying layers which contain different therapeutics is mentioned, for example a combination of antibiotics and growth factors [23].

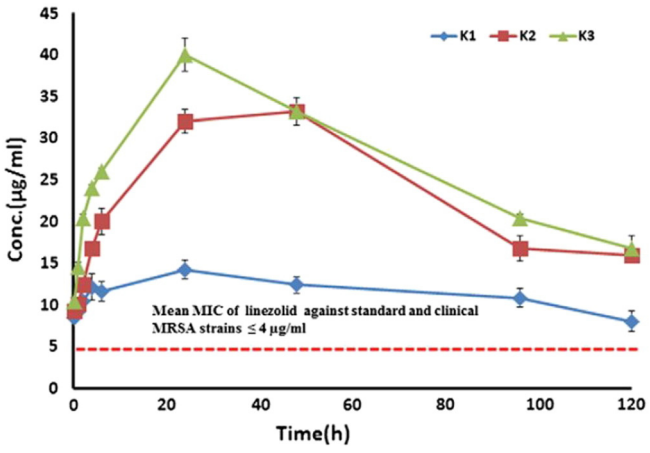


Fig. 5. Concentration profiles of drug released from K-wires. Three drug/polymer mixtures used: 2.5%, 5% and 10% indicated by K1, K2 and K3 respectively. Reproduced from [22].

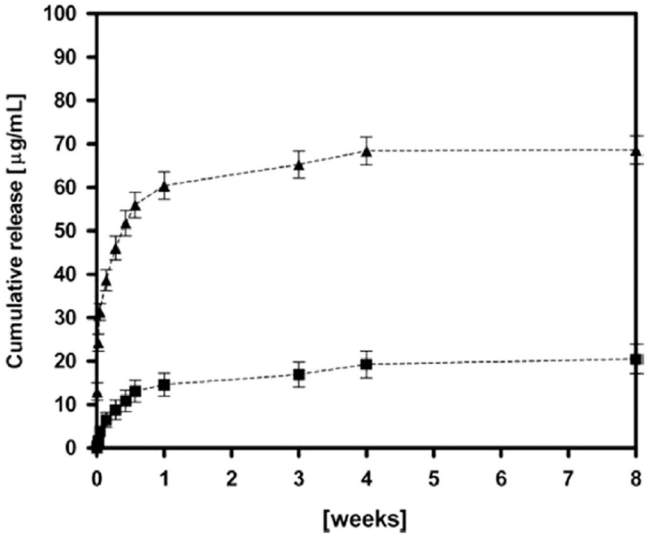


Fig. 6. Cumulative release of the drugs from PLDL disks coated with PLLA. The drugs Dexamethasone (DM) (▲) and Eugenol (EG) (■) were considered. Reproduced from [9].

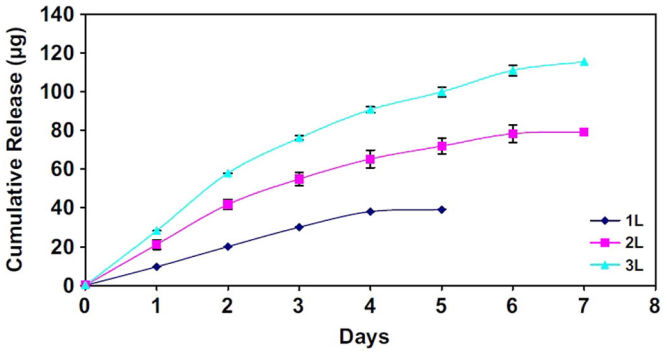


Fig. 7. Cumulative release of vancomycin from sol-gel films with different layers (L). Reproduced from [23].

Song et al. [17] fabricated a polycaprolactone (PCL)/polyvinyl alcohol (PVA) core-sheath nanofibre (NF), blended with hydroxyapatite nanorods (HA) and type 1 collagen (Col) via an electrospinning technique [17] (Fig. 1, Image 3). The PCL/Col mixture acted as a suitable outer barrier, referred to as a "sheath" in the experiments, since it degrades slowly [17]. The mixing of HA to the PVA increased surface roughness and the mechanical strength of the NFs. This mixture was the core of the NFs and was designed to mimic bone tissue and act as a drug reservoir.

Controlled release experiments of Doxycycline (Doxy) and Dexamethasone (Dex) (an antibiotic and an anti-inflammatory respectively) were carried out to evaluate the NFs as a coating. To assay the release of Dex and Doxy from the NFs, samples of NF were soaked with distilled water and the concentrations of Dex and Doxy were measured via a spectrometer. In both experiments, release media was not renewed or stirred. PCL and PVA fibres were used separately initially to assess their bactericidal ability and then combined to form a core-sheath NF structure. The results of the experiments showed that PVA fibres blended with Doxy had a burst release of drug within the first 10 h, with complete release within 48 h. However, when a PCL sheath was included in the NFs, the duration of release of Doxy was increased to over 700 h, due to slow degradation of the PCL sheath [17]. When Doxy was applied to both the core and the sheath of the NFs, the bactericidal effect was found to be long lasting, the release of Doxy from the core-sheath NFs were able to provide sustained Doxy release for at least 152 h [17]. Dex showed similar release behaviour to Doxy when blended with PVA, i.e. a burst release within 10 h and complete release within 48 h. With a PCL sheath added, Dex release was found to have increased to over 150 h, with a slightly further increase to release duration when Dex was also added to the PCL sheath.

The authors concluded that their experiments showed that the NFs produced were capable of controlling the release of Doxy and this was successful in inhibiting MRSA colonisation and preventing possible infection in vitro. It was also shown that the NFs displayed good biocompatibility and osteoconductivity, through the measure of cellular adhesion to the NFs.

2.3. Surface and structure alterations of orthopaedic implant materials for drug release

An area of research that has gathered much attention is materials from which orthopaedic devices will be manufactured. This is a rather complex area of study as many characteristics of a proposed material and the resulting impact on the body have to be considered. The material must display a suitable set of mechanical properties, such as compressive/tensile/fatigue strength and density and of course the material must not induce a toxic effect. The precise application for the material will also play a role in its suitability, for example, the material may require greater wear or corrosion resistance than others as it may have to be situated in adverse conditions in the body [2]. Altering the surface of an implant to produce nanotubes, for example, has many advantages. As well as acting as drug reservoirs on the implant surface [2,13,15,19], the strong mechanical properties of some nanotube structures can be used to reinforce implants [13,19]. Additionally, it has been hypothesised that nanotubes made of metal oxides or alloys may improve osseointegration [13,15,19] and cell viability [15,19,21], by the fact that the rougher surface is more akin to bone than implants with a smooth surface [13,15,18,19].

Aninwene et al. [18] examined the effect of a drug-coated anodised nanotubular surface on osteoblasts (Fig. 1, Image 4). Anodised nanotubes increased the roughness of the surface of the titanium in their experiments which resulted in the titanium having a surface which is similar to natural bone. Osteoblasts tend to adhere to surfaces which are likened to bone, in terms of chemistry and roughness, and it is precisely this which inspired their research [18]. They also noted the potential for these nanotubes to act as reservoirs for antibiotic, anti-inflammatory and bone-growth promoting drugs [18]. The authors also note that there are possible surface tension issues that could impede drug loading and noted that when soaked with SBF, the calcium phosphate crystal formations on the titanium surface may provide optimal surface energy to efficiently coat the anodised nanotubular titanium samples with drugs.

In their experiments they prepared anodised and non-anodised samples of titanium and coated them with drugs, either penicillin/streptomycin or dexamethasone via simple physical adsorption or by soaking the samples in SBF, which contained the drugs. They also seeded osteoblasts onto the samples which were then cultured. Their results showed that osteoblasts adhered in greater numbers to the anodised titanium than the non-anodised (Fig. 8) and that the samples which were soaked with SBF containing the drugs eluted more penicillin/streptomycin and dexamethasone than samples which were coated by simple adsorption. This experiment has very encouraging results: the combination of better osteoblast adhesion and drug-elution from a nanotube structured titanium surface is a potential way to combat the issues related to the use of OIs.

Lyndon et al. [2] have reviewed several of the latest metallic and drug/device combinations and outlined some promising materials for use in orthopaedic applications, in particular a porous magnesium foam was mentioned. Aghion et al. [20] examined the viability of drug carrying and release from a magnesium foam. They used a magnesium alloy which was reduced to a powder for the milling process to obtain the magnesium foam. The level of porosity of the foam was controlled by using different quantities of ammonium hydrogen carbonate (spacer), with varying diameters, and mixing this with the magnesium alloy powder. Once the resultant powder was in the final stage of processing, the ammonium hydrogen carbonate evaporated due to the high temperature. Mixtures containing 10% and 25% spacer material was used. The authors noted that the average pore size in the magnesium foam when 25% spacer material was used, was around 140 μm and with 10% spacer material it was 40 μm. It was also found that using a mixture with 25% spacer material, produced a foam with significantly more interconnected pores, whereas the 10% spacer mixture only had interconnected pores close to the surface, thus limiting its ability to carry and release a significant amount of drug [20]. The magnesium foams were loaded with the antibiotic gentamicin by immersing the foams in a concentrated gentamicin solution, then evaporating the water to leave behind solid gentamicin within the foams.

The foams were placed into PBS solution and the concentration of gentamicin was measured. It was found that the release of the drug from magnesium foam made with 10% spacer was relatively quick and could be explained by the lack of interconnected pores throughout the foam, with such pores only being present close to the surface of the foam. The magnesium foam made with 25% spacer had considerably

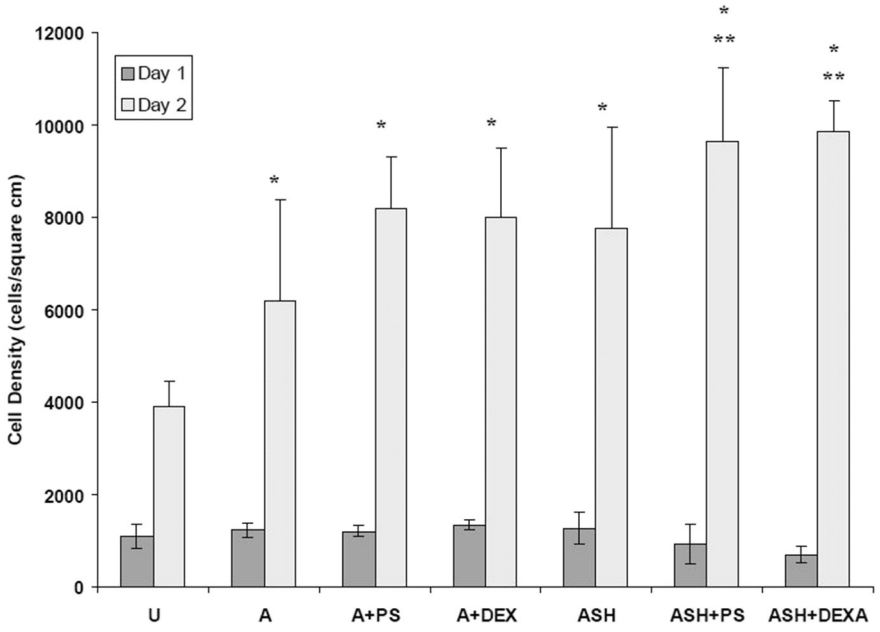


Fig. 8. Osteoblast density after culturing for 1 and 2 days, following drug release from anodised nanotubes. Abbreviations: U, unanodised Ti; A, anodised Ti; A + PS, anodised + penicillin/streptomycin physical adsorption; A + DEX, anodised + dexamethasone physical adsorption; ASH, anodised, heat-treated and SBF-soaked Ti; ASH + PS, as previous but with penicillin/streptomycin; ASH + DEXA, as previous but with dexamethasone. Notes: Data = Mean ± SEM; $n = 3$; $^{*}p < 0.1$ compared to unanodised Ti; $^{**}p < 0.1$ compared to the respective drug coated via physical adsorption. Reproduced from [18].

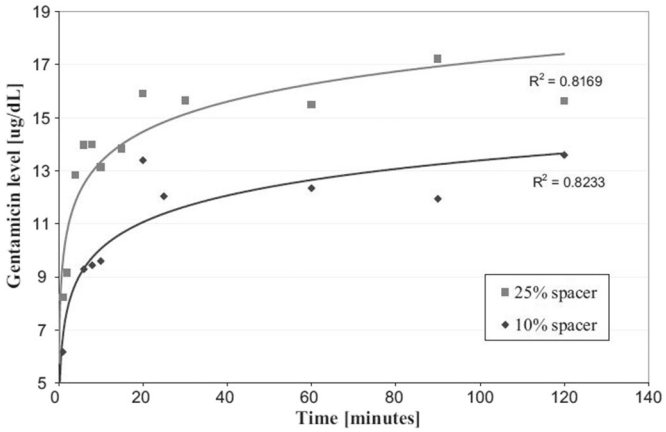


Fig. 9. Concentration profiles of gentamicin release from magnesium foams with 10% and 25% spacer material. Reproduced from [20].

more interconnected pores, a greater level of porosity and so was able to absorb more drug (Fig. 9).

The degradation of the magnesium foam was found to rise by increasing spacer content, which was expected since using more spacer increases the surface area of the foam and so a greater area is exposed to the PBS solution [20]. The experiment demonstrates that the overall porosity of the material can be altered depending on the amount of spacer used. However, Aghion et al. note that the reduced time for complete degradation of the magnesium foam limits its use to applications where drug release is required for a limited time [20].

3. Mathematical methods

To the best of our knowledge, no mathematical models exist in the literature which focus *specifically* on therapeutic delivery from OIs. This is somewhat surprising since, there are countless examples of where mathematical modelling has been used effectively in other drug release applications. Some of these studies focus on a specific drug-releasing implant (e.g. coronary stents), whereas others focus on drug release from particular materials or structures, many of which are candidates for OIs. Therefore, it is entirely possible that several existing published models will find application in designing enhanced OIs, whilst others, with some modifications may also prove useful. With the growing acceptance that the release of drugs from OIs is the future, it seems sensible to learn from the development of more advanced drug-releasing implants. Using the example of coronary stents, in the early days a purely empirical approach was adopted to device design, with the focus on a combination of in vitro and in vivo animal experiments. However, it quickly became apparent that the use of mathematical and computational modelling could not only reduce the number of experiments, but also save on the costs and time associated with additional experiments [25,26].

It is useful, however, to remember that a mathematical model, much like an experiment, is an approximation tool: if a model of the release of a drug from an implant fits experimental data well, it may not capture the whole picture, as simplifications are usually required. A mathematical model that has great predictive qualities can be a significant contribution to the understanding of the bigger picture and confidence in a model is enhanced by altering the experimental conditions and then comparing to the predicted results. Once validated, the parameters within the model can also be varied and the resultant release profiles compared, without the need to rerun experiments [25,27].

3.1. Drug release mechanisms

To model drug release mathematically, one must have a level of understanding of the mechanisms of drug release within the particular system. This can be tricky to pin down, however, by comparing the results of an initial model with experimental data, it is often possible to ascertain whether additional mechanisms need to be included, or indeed removed from the model. Drug release from a medical device may be facilitated by a number of mechanisms, such as diffusion, swelling, dissolution, convection, erosion and degradation, amongst others, although in reality it is likely a combination of mechanisms that govern drug release [25,26,28].

Fredenberg et al. [29] note that there is some ambiguity with the term "release mechanism": in some cases, it is regarded as the way drug molecules are transported or released and in others; it is a description of the processes which influence the release rate. For example, they note that the release mechanisms in poly(lactic-*co*-glycolic acid)-based (PLGA) devices are diffusion, osmotic pumping and erosion. The release rate is usually said to be diffusion-driven firstly and then controlled by degradation/erosion in the later stages [29]. However, it is stated that more knowledge is required to form the bigger picture of these mechanisms and that comes from the understanding of the underlying processes which drive them, such as water absorption, hydrolysis and erosion [29]. The authors state that for PLGA-based systems, there are only four ways for drug to be released: 1) transport through the polymer; 2) transport through water-filled pores; 3) erosion of the polymer encapsulating the drug; and 4) osmotic pumping [29]. From these routes of drug release, a much larger system of processes which influence them can be found. However, it is often the case that the level of detail required in the mathematics, to adequately capture the release profile, is relatively small.

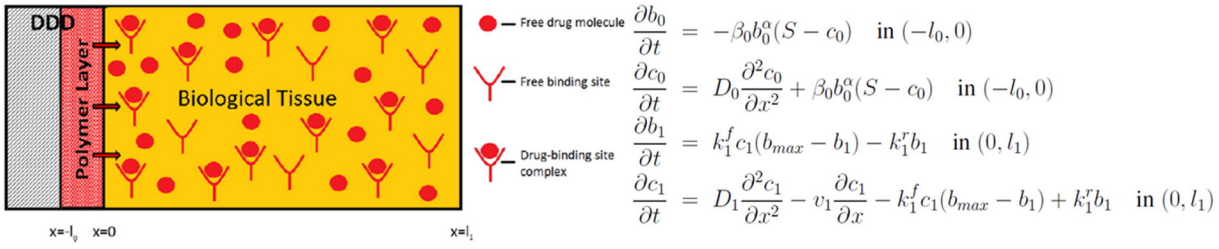
3.2. Some existing mathematical models describing release mechanisms

There are, of course, countless mathematical models describing release mechanisms, covering a whole range of applications. Here we mention two particularly relevant publications. McGinty and Pontrelli [30] recently provided a general model of coupled drug release and tissue absorption which may be applicable to certain OIs (Fig. 10). Their flexible model allows for the consideration of both dissolution and diffusion within a durable polymer coating, with the former depending on both the dissolution rate and the solubility of the drug. The model does make a number of assumptions, including an idealised one-dimensional geometry and the polymer is assumed to be instantly fully wetted following insertion. However, in contrast to much of the drug delivery literature, their model importantly accounts for drug transport within tissue following release. Such a model, which incorporates the biological environment, is likely to be crucial if in vivo release is to be modelled. Their model of drug transport within tissue is very general and can be used in cases where diffusion and/or convection and/or binding are at play. A number of binding mechanisms can be accounted for, including nonlinear saturable irreversible binding; linear reversible binding and; linear irreversible binding. Therefore, this model can potentially predict the binding of drugs released from OIs or other implants to biological tissue. Special cases of the model are given and it is noted that particular circumstances could arise in which a process is insignificant in contrast to the others. For example, if the drug has a very high solubility and/or a very low initial concentration, the drug will promptly dissolve and so a diffusion model is sufficient [30]. McGinty and Pontrelli provide a case study in which the model is applied to a drug-eluting stent (DES) (a stent is a mesh-like supporting scaffold that is inserted into arteries where blood flow has become unsafely restricted [27]). When compared with in vivo experimental data, the model showed good agreement [30].

Lauzon et al. [31] reviewed growth factor delivery systems and listed numerous existing mathematical models that could potentially be used to model growth factor release. In contrast to the model of McGinty and Pontrelli, all of these models account for drug release only, and do not model drug transport post-release. The mechanistic and semi-empirical/empirical models presented are based on the drug transport mechanisms of diffusion, swelling and erosion. Another mechanism, in which both mechanistic and semi-empirical models are listed, centres on the possible interactions between the drug and the device: these are known as "Affinity-based models" [31]. The limitations of the models provided generally revolve around the assumptions, such as perfect sink boundary conditions and constant diffusivity. Other drawbacks are mentioned, which highlight that some models do not capture the influence of certain processes, such as depletion of the drug through biological interactions.

It is worth mentioning that the presentation of the models by Lauzon et al. may encourage a "pick and mix" approach to mathematical modelling, where one would simply select a model based on the circumstances of a particular system. Whilst in many cases this could be appropriate, we urge some caution: the tabulated models do not always provide sufficient details regarding the assumptions that were made in deriving the equations. For example, the models are all one-dimensional, yet no detail is provided as to the validity for an arbitrary device geometry and it is not always clear what experimental conditions are considered, e.g. stirred, unstirred, infinite sink, etc. It is recognised by the authors that the models may not, in fact, be suitable for growth factors. One important difference is that growth factor proteins can be much larger than drug molecules [32] and so particle size considerations may need to be taken into account. Mathematical modelling is flexible, but careful consideration of the release mechanisms, the geometry of the proposed device and the experimental conditions, must be accounted for. Although general models do exist in the literature (e.g. Lauzon et al. and McGinty and Pontrelli), they are general only for a particular set of circumstances and conditions. Even when a mathematical model exhibits great predictive qualities for a particular system, a change to the device, such as a change of material or geometry, or a change to the experimental setup such as choosing to stir the release medium, may not allow for such a model to maintain its usefulness, and in these circumstances a new model may need to be devised.

In spite of the intricacy of the processes that can occur in a drug delivery system, mathematical modelling can be a light at the end of the tunnel. Carefully considering the underlying processes mathematically can lead to the confirmation or discovery of the main processes that drive the mechanisms of drug release. Some processes may have a much greater influence on the release rate than others and so it is important to identify them if we seek to attain controlled release for a particular application.



$$\frac{\partial b_0}{\partial t} = -\beta_0 b_0^{\alpha}(S - c_0) \quad \text{in } (-l_0, 0)$$

$$\frac{\partial c_0}{\partial t} = D_0 \frac{\partial^2 c_0}{\partial x^2} + \beta_0 b_0^{\alpha}(S - c_0) \quad \text{in } (-l_0, 0)$$

$$\frac{\partial b_1}{\partial t} = k_1^f c_1(b_{max} - b_1) - k_1^r b_1 \quad \text{in } (0, l_1)$$

$$\frac{\partial c_1}{\partial t} = D_1 \frac{\partial^2 c_1}{\partial x^2} - v_1 \frac{\partial c_1}{\partial x} - k_1^f c_1(b_{max} - b_1) + k_1^r b_1 \quad \text{in } (0, l_1)$$

Fig. 10. A general model of coupled drug release and tissue absorption [30]. Bound drug and free drug are represented by b and c, respectively, whilst the subscripts 0 and 1 refer to the drug-containing coating of thickness l_0 and biological tissue of thickness l_1, respectively. The parameters β_0, S, D_0 represent the dissolution rate, drug solubility and drug diffusion coefficient whilst $0 < \alpha < 1$ depends on the dissolution model studied. D_1 and v_1 are the diffusion coefficient and magnitude of convection in tissue, whilst k_1, k_{-1} and b_{max} are the binding on and off rates and the density of binding sites, respectively. Full details, along with boundary, interface and initial conditions can be found in [30].

3.3. Mathematical modelling of drug release from some potential OI materials

Tzur-Balter et al. [33] experimented with drug release from mesoporous silicon and then sought to mathematically model the release of the drug. In their experiment, they measured the release of the anti-cancer drug Mitoxantrone (MTX) from two samples of mesoporous silicon, one in an unaltered form (PSi) and the other chemically altered using 1-dodecene (d-PSi). The chemical altering process is hydrosilylation, in which the surface of the silicon is bonded with hydrogen, resulting in a more stable silicon platform [34]. The samples were loaded with MTX and placed into PBS solution. Measurements of the released drug were taken by sampling the media and then replacing it with fresh PBS solution. Their results showed that the chemically altered silicon sample (d-PSi) sustained release for much longer and that the sample had eroded far less than the PSi sample. It was hypothesised that, based on the results of the experiment, the release of MTX from the PSi sample was by the combination of two mechanisms, those being diffusion of MTX and the erosion of the sample [33]. The other sample, d-PSi, had not eroded nearly as much and so the release rate of MTX was slower. The authors concluded that since the release of MTX was much quicker than the erosion in the case of the d-PSi sample, the governing mechanism of release of MTX from this sample was diffusion [33].

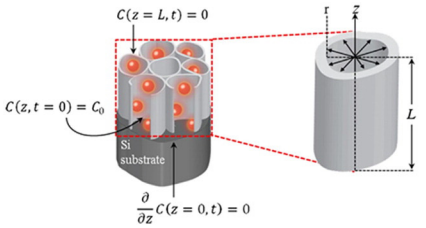
To mathematically model this experiment, a relatively simple model which combined the erosion of the samples and diffusion of the drug was devised. Fick's second law with a uniform, constant drug concentration as the initial condition, and infinite sink and zero-flux boundary conditions were proposed (Fig. 11). The fraction of mass of drug released in the experiment is given by Crank's classical solution [35], which Tzur-Balter et al. modified to include the effects of the erosion of the porous wall of the silicon. It was assumed that the diffusivity was the only parameter in the bulk porous domain that experiences significant changes due to erosion and so the fractional drug release equation was altered to include this effect. Diffusivity was modelled by defining a function $\sigma(t)$ which took erosion into account.

The model was found to fit the data obtained very well. To increase the validity of the model, the release profiles obtained from the unaltered Crank model and a model which did not account for erosion and the other processes which affected diffusion, were added to the plots. These two models did not fit the data well, both of which overestimated the release of MTX in the early stages of release and both underestimated MTX release, after approximately 2 h with the PSi sample data. For the d-PSi sample data, both of the models in this case overestimated MTX release between 15 and 70 h [33]. To show that their model is adaptable, the authors plotted the model alongside existing experimental data [36] of dexamethasone release from dodecyl modified porous silicon samples. Their model was able to fit this data well, but it was noted that had there been data on the mass change in the silicon samples due to degradation, the model would have had a more accurate fit as the erosion of the samples would have been better approximated [33].

Kumeria et al. [14] monitored drug release from nanoporous anodic alumina (NAA) under dynamic flow conditions (Fig. 12). In the experiment, high-purity aluminium foils were obtained and prepared so that a self-ordered nanoporous layer was achieved, with a pore diameter range of 30–35 nm and a pore length of, approximately, 4.5 μm [14]. Indomethacin (an anti-inflammatory drug) was loaded in three different ways into the NAA samples: 1) drug was load into the pores and the surface of the NAA sample; 2) drug was loaded solely into the pores of the NAA sample; 3) drug was loaded only on the surface of the NAA sample [14]. Kumeria et al. used reflectometric interference spectroscopy to monitor the release of the drug from the NAA samples, whilst also exposing the samples to varied fluid flow rates, those being 0, 10, 30 and 50 μL/min. The fluid used was PBS solution [14]. The inspiration for this approach to assess drug release is due to drug release evaluation being commonly carried out in a batch observing process under static conditions, which is limited in that it does not capture the in vivo effects on drug release [14]. In static experimentation, the release media is continuously receiving drug and will eventually become saturated and so the concentration gradient between the drug-eluting sample and the media will be reduced. This reduction will have an effect on the overall rate of drug release, potentially giving inaccurate results and so monitoring drug release under dynamic flow conditions should help reduce the inaccuracy of the data whilst improving the simulation of in vivo drug release.

The results obtained from the experiments were compared to data of drug release from NAA samples under static conditions and theoretical values obtained from a modified Higuchi equation in an attempt to identify the governing mechanism of drug release [14]. Under the static conditions the results show a burst release of the drug from the NAA sample, during which 75% of the drug was released in the first 100 min of the experiment. The release was then steady for the next 4 days, during which 100% of the drug had been released [14]. The Higuchi equation is founded upon Fick's second law and models the release of drug from insoluble matrices [14]. Assuming perfect sink conditions and that the initial drug concentration is significantly higher within the drug-releasing device than the surrounding media, the Higuchi equation can describe diffusion controlled release of both water soluble and poorly water soluble drug from non-degradable porous devices [14].

The rate of drug release was confirmed to be inversely proportional to the square root of time [14], which is obtained from the Higuchi equation automatically. Fitting the model to the release data, Kumeria et al. were able to ascertain the release rates under dynamic flow. It was noted that at a flow rate of 50 μL/min, the drug release rate was approximately 4 times that of drug release in static conditions. However, at the lower flow rates, 10 and 30 μL/min, the drug release rates were comparable to the release rate in static conditions. The authors concluded that a faster flow rate increased the amount of drug release from the NAA implants and with the results of the experiment and the simple mathematical model, it was established that fluid flow can have a significant influence on the release rate [14]. The high values of the coefficients of



$$q(t) = 1 - \frac{m(t)}{m_0} = 1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}(2n+1)^{-2}\exp\left[-\left(\frac{2n+1}{2L}\right)^2\int_0^t \sigma(t)dt\right]$$

Fig. 11. Illustration of a mathematical modelling approach for drug release from porous silicon. Boundary and initial conditions are shown. Reproduced from [33]. The cumulative fraction of drug released is given by q. The parameter σ represents a time-dependent diffusivity as a result of opening pores. L is the film thickness, while $m(t)$ and m_0 are the mass of drug in the pores at time t and the initial mass respectively [33].

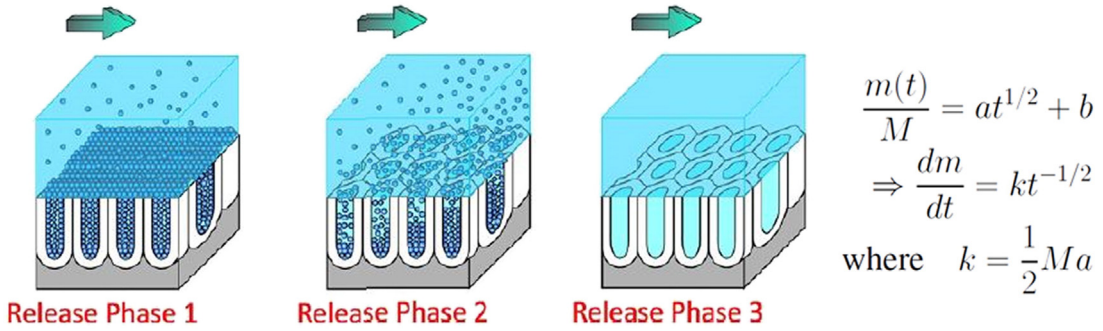


Fig. 12. Illustration of drug release phases from nanoporous alumina under dynamic flow. Reprinted with permission from [14]. Copyright (2013) American Chemical Society. The simple model used is a modified Higuchi equation where $m(t)$ is the mass of drug released at time t, M is the initial mass of drug and a and b are fitting parameters. The rate of drug released is expressed in terms of a parameter k, which was found to vary for different flow rates [14].

determination from the model fitting, validate that drug release is dependent on the square root of time, which is a key trait of Fickian diffusion [14].

3.4. Mathematical modelling of drug release from porous structures

McGinty et al. [37] adopted a mathematical approach to predict planar drug release from bulk nanoporous materials, and showed that drug release from nanotubular and smooth surface systems emerged as special cases. Whilst their focus was on polymer-free DES, it was noted that the models could in principle be applied to drug release from nanoporous drug-releasing implants in general. Their model assumes that the drug dissolves on a moving front, before diffusing through water-filled pores and into the release medium (Fig. 13). Additionally, the possibility that drug may adhere to the walls of the pores is accounted for through a linear reversible reaction.

Despite these intricacies, a well-posed initial boundary value problem was formulated and the resulting moving boundary problem was solved analytically. One of the advantages of their approach is that they were able to derive an analytical solution, allowing for direct calculation of the release profile of the drug [37]. A model for the two-stage release from a layer of drug on a DES surface and then the subsequent release from a nanoporous layer containing drug [37] is also provided. The key parameters of the system which have a dominating influence on drug release are identified and design considerations are provided so that a release profile may be tailored to suit the particular application.

By making the assumption that the absorption and desorption rates are much quicker than the rate of diffusion (the "equilibrium assumption"), the authors derived a one-dimensional form of Fick's second law, where the diffusion coefficient is referred to as the apparent diffusion coefficient and this single parameter takes into account the effects of porosity, absorption, desorption, tortuosity and constrictivity [37]. Both stirred and unstirred cases were considered for the model. One of the key findings was that dissolution is an order of magnitude faster in stirred conditions compared with unstirred: this conclusion directly arose from mathematical analysis of the underlying equations.

3.5. Mathematical modelling of drug release from stents and lessons to be learned

One of the key areas where mathematical modelling has greatly enhanced understanding of drug release and the mechanisms that control it, is in simulating drug release from stents. Using a mathematical approach in tandem with experimentation, researchers have been able to model drug release from a variety of stents [27], and ascertain the dominant mechanisms of release. We refer the reader to a recent review [27], where modelling efforts are summarised in the three categories: 1) models of drug release from durable and biodegradable polymer coatings; 2) models of drug uptake into arterial tissue, encompassing advection-diffusion-reaction; and 3) models of coupled drug release and tissue absorption. Both simple and more sophisticated models covering analytical and numerical solutions are described, ranging from 1D single layer convection-diffusion systems to 3D multilayer systems encompassing anisotropy, nonlinear saturable binding and coupling with lumenal flow. This review highlights that the model required for a given application must reflect the conditions of the experiment which the produced the comparison data. The importance of modelling and experiments being simultaneous approaches is stated and it is stressed that the accuracy of the outputs of a model are only ever as good as the accuracy of the inputs, especially when the model is particularly sensitive to changes in one or more parameters.

Sirianni et al. [38], for instance, modelled the drug release from a commercially available stent and they noted that Fickian diffusion, dissolution and osmotic gradient models were able to fit the data of their experiments well. A good fit to the data was also achievable by varying the parameters of the model, despite some parameter values being unrealistic [38]. This only serves to highlight that care must be taken not only when devising models for a particular application, but also when

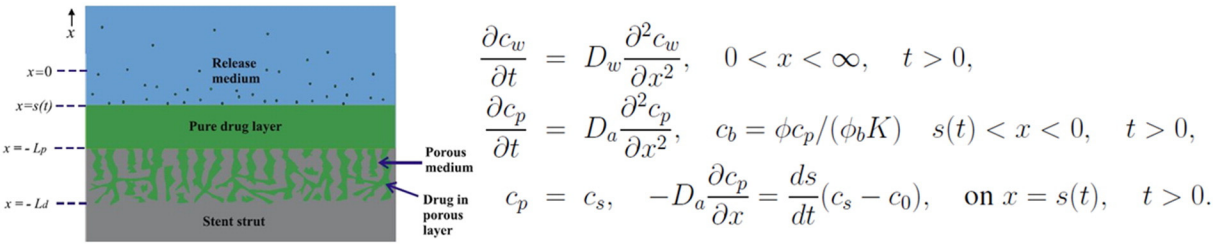


Fig. 13. Illustration showing an idealised mathematical model of drug release from a bulk nanoporous layer coated with a pure drug layer. Reproduced from [37]. In the model c_w, c_p and c_b represent the concentrations of drug in water, pores and bound to pore walls, respectively. D_a and D_w are the apparent and free diffusion coefficients of drug, K is the equilibrium dissociation constant, c_s is the drug solubility and ϕ and ϕ_b are porosities. The parameter s is the location of the moving boundary, expressed in terms of the classical Stefan condition. The dissolution of the pure drug layer is given in terms of error functions, whilst the drug release from the pores is solved numerically, making use of continuity of concentration and flux at $x = -L_p$ [37].

interpreting the results of the model, especially if several parameters have been estimated inversely. If a model has several parameters, it may fit experimental data well but with the subsequent addition of other parameters, the confidence in the model is reduced [38]. An alternative is to employ a simpler semi-empirical approach (e.g. Peppas [39]) which includes a smaller number of (non-physical) parameters. However, a mechanistic modelling approach has a clear advantage over a semi-empirical approach since the parameters of the model may (in principle at least) be measured experimentally and once validated, a mechanistic model may be used in a predictive capacity.

Stents are similar to OIs in terms of drug release mechanisms and possible coatings, however, the biological environment is different. For example, stents experience pulsatile blood flow, whereas an orthopaedic device may experience an environment in which the main issue is mechanical loading. However, the differences in biological environment between stents and OIs does not preclude the use of mathematical modelling. Indeed, mathematical modelling has been used in many other drug delivery applications where the drug is exposed to varying environments. For example, in transdermal drug delivery [40], the drug is not exposed to appreciable flow, but is faced with the significant barrier provided by the stratum corneum before it can reach the capillary beds; in ocular drug delivery [41] the drug is exposed to the continuous flow of the lacrimal fluid of the eye; and in drug delivery from tablets [42], the drug is surrounded by the fluid of the stomach and gastro-intestinal tract. Yet in each of these cases, mathematical modelling has been used to predict drug release and to help optimize device design. Quite often, however, as a result of the huge expense and time associated with in vivo experiments, drug delivery device manufacturers and experimentalists routinely test the release of drug in an in vitro environment, under static or gentle agitation conditions, irrespective of the actual biological environment for the application in question. While these conditions are unlikely to accurately replicate the in vivo situation, they nonetheless provide one with an idea of the shape of the release profile, allowing for comparison between different device designs. Furthermore, it allows for the repeatability of the release profile to be tested. In addition, when compared with appropriate mathematical models of the in vitro experiment, insights can be gained into the mechanism(s) of release. Therefore, mathematical models which simulate drug release under static or gentle agitation conditions can still form an important part of the overall drug release characterisation and release mechanism understanding process. However, one should not underestimate the importance of properly accounting for the biological environment when the intention is to compare with in vivo data. Bozsak et al. [43], realising this, coupled their model of drug release from stents with flowing blood in the lumen and drug binding in tissue. They acknowledge that to be able to truly optimize stent design, then such an approach is necessary.

The current literature highlights the benefits and obstacles of OIs; however, they are not insurmountable. Drug release from stents was scrutinised greatly via experimentation and mathematical modelling, but it has paid off and so perhaps it is time to use mathematical modelling of orthopaedic devices to simulate drug release and provide optimal implant design strategies.

4. Discussion

As we have seen, there are a plethora of experimental approaches in the literature focussed on examining the potential of drug release from OIs; however, to the best of our knowledge, there are no mathematical models of drug release specific to OIs. In many cases, questions arise which may not be answered with repeated experiments alone. Moreover, in several of the studies, the authors alluded to theoretical explanations of observed phenomena which they were not able to substantiate with the experiments alone. We are advocating that mathematical modelling could be extremely useful in many of these cases. A mathematical model would have to consider the experimental setup in detail and include the various parameters that define the experiment. With a suitable model, the outcome of a change in the experimental setup could be predicted, without the need to rerun costly experiments. A validated model may also help identify the dominant mechanism of drug release and aid in establishing the relationships between different parameters and variables.

It is worth considering a *coupled* model as although it is important to understand the release of drugs from OIs, it would be wise to have an understanding of the biological environment, including drug/tissue interactions, as this may affect drug release. With these points in mind, we suggest that experiments should be conducted *in tandem* with mathematical modelling. We stress that as well as helping to characterise drug release from potential OIs, future experiments must focus on defining the desired in vivo release profile for the intended application. It should be noted that the mathematical modelling of growth factor release is possible, however, careful consideration must be given since the size of an individual protein molecule can be much greater than that of a drug molecule. This may have implications in terms of delivery from nanostructures and in the derivation of the underlying transport equations.

The experiments conducted by Gimeno et al. [11] and Perez et al. [12] feature prototype implant designs with a view to acting as drug-eluting pins and screws for fixation applications. In these cases, it is important to consider the geometry of the device. The designs used in the experiments were very similar and if an orthopaedic device were to utilise the ideas of these experiments, they would not necessarily be smooth on the outer surface i.e. a fixation screw would have threading and it would be prudent to consider the affect this may have on the release profile of the drug. The authors have experimentally identified parameters which may, in principle, be incorporated into a model, subsequently varied and then the resulting effect can be observed without the need for more experiments. Also noteworthy is that these experiments additionally focus on the effectiveness of the drug release in combating bacterial infection associated with orthopaedic surgery. A coupled mathematical model of biofilm formation and drug release could help to understand biofilm development in tandem with the controlled release of antibiotics. This approach could provide important insights such as revealing the timescale over which the bacteria would be vulnerable to antibiotic treatment and perhaps the necessary drug concentration and delivery strategy to eradicate them.

Another factor to consider from these experiments is drug solubility. In [10,11], the drugs are used in the form of a dry solid and in [11], two drugs of significantly different solubility are used. Since the drug must dissolve before diffusing out of the device, this process may have an important impact on the rate of release and perhaps explains the quite different release profiles observed for the two drugs considered [11]. A mathematical model which includes the dissolution process could not only potentially explain these differences, but also predict the release profile for other candidate drugs of different solubility, without having to conduct numerous experiments. One further question that arises from the experiments in [11] is that the release profiles for both drugs in the 2 orifice case, have very similar release profiles, which is perhaps counter-intuitive. A mathematical model may be able to establish the connection between drug release and the number of orifices available for release. One could say that with more orifices, drug release will naturally occur more quickly, however, there may be other factors that may not be easily identifiable from experimentation alone.

A common feature of the experiments reviewed in this paper is porosity, namely within [10–12,20]. These experiments in some way have drug diffusing through a porous structure which could be altered to achieve the desired release profile. However, the properties of the particular material/device in question will determine the way in which a mathematical model accounts for the porosity. For example, Gimeno et al. [10] consider a porous tube, through which the drug can diffuse, on the other hand, Aghion et al. [20] have the interconnected pores of the magnesium foam containing drug, which open up as the material

degrades and so the relation of porosity to drug release is dependent on the setup. With a particular system in mind, a mathematical model could establish the importance of porosity in drug release and could also allude to how to fine-tune the porosity to suit a specific application.

Biodegradable coatings also feature heavily in the literature, the experiments which examine this phenomenon in this review are [9,17,22,23]. Drug release in these setups are especially influenced by the degradation of the coatings used, be they nanofibres, polymers or gels. As such, a mathematical modelling approach could make use of moving boundaries to simulate the degradation of coatings suitable for OIs. Nanotubes for orthopaedic applications have also been examined and they are a promising method of drug delivery. Aninwene et al. [18] experimented with them and noted that they can act as drug reservoirs. Although these may not degrade like the coatings mentioned above, a mathematical model utilising a moving boundary may prove useful, since fluid penetration will deplete the drug contained in a nanotube.

The mathematical modelling conducted by Tzur-Balter et al. [33] is a good example of highlighting the benefits of modelling. A mechanistic model can account for several system characteristics and potentially provide insight into the interactions of different drug transport phenomena. In the case of Tzur-Balter et al., the time dependent degradation of the porous structure of the silicon samples was modelled and given that the model has considerable validity, it captures the essence of drug release in this particular setting. It establishes that degradation is a dominant mechanism of drug release in these experiments. The model presented by Tzur-Balter et al. has many parameters and although increasing the number of parameters may complicate a model, it does not diminish its usefulness. In fact, doing so can allow one to deduce which aspects of a system have greater control on drug release. The introduction of more parameters into a model can provide greater degrees of freedom which can be beneficial as tailoring the drug release profile means it can suit a wider array of applications.

The experiment conducted by Kumeria et al. [14] also illustrates the benefits of mathematical modelling approaches to drug release. In this instance, the experimental method of evaluating drug release using reflectometric interference spectroscopy whilst under fluid flow conditions was validated as the results from the experiments in static and dynamic conditions were well represented by the modified Higuchi model. Kumeria et al. concluded that diffusion was the governing mechanism of release. Backed up by the mathematical approach and the experimental findings, they concluded that evaluation of drug release under dynamic conditions results in a better understanding of the release from drug delivery platforms utilising a nanoporous layer. It is of great importance that the mechanisms of drug release are understood as it allows for the design optimisation of drug-eluting devices. More applicable experimental methods that simulate in vivo conditions and the simultaneous mathematical understanding of drug release will allow this to be attainable. The in situ drug release measurements of Kumeria et al. are particularly appealing. Traditionally, drug release typically was measured by taking samples from the release medium at various time points and analysing using either HPLC (High Performance Liquid Chromatography) or UV mass spectroscopy. Neither of these methods are ideal, since the removal of drug from the release medium alters the concentration gradient and consequently is likely to affect the flux of drug leaving the device. An alternative is to remove the device from the release medium, which is then analysed. However, some of the drug close to the surface of the device could potentially be excluded, resulting in errors in the calculation of drug mass. Neither approach can easily provide the spatial distribution of drug in the release medium. A number of new technologies are emerging which potentially will provide more accurate measurements, non-destructively and in situ. Some examples include imaging mass spectroscopy [44], fibre optics [45] and photometers [46].

Although a mathematical modelling approach could provide valuable insight into drug release across a wide array of orthopaedic devices, one must not forget that it is often the case that increasing complexity may require a numerical solution. This does not diminish the usefulness of mathematical approaches; however, it is often the case that simpler models that give rise to analytical solutions can be of more practical use. The ability to achieve analytical solutions is greatly advantageous as release profiles can be plotted immediately and from these solutions, one can deduce the governing parameters of drug release. However, it is usually the case that the setup being modelled has to be simplified in order to obtain an analytical solution. One may have to use an idealised geometry for example, provided there is justification. If the net transport of drug from a device is in one direction, or particular features of the geometry are much greater in size, relative to others, then it may be suitable to have a mathematical model based on one spatial dimension. This may seem like a drastic simplification but it is often justifiable mathematically. An important point to make is that many of the experiments are conducted in vitro and a useful mathematical model of drug release from OIs should account for the underlying biological environment. Release profiles obtained via in vitro experiments are not necessarily the same in the in vivo case, however, experiments in vivo will help define what the release profile should be and from this the mathematical tools available can be put to good use to help in the designing of drug-releasing OIs.

5. Conclusions

In this review we have highlighted some of the key issues from the use of OIs and have provided examples of experimental approaches to aid in the understanding of drug release from OIs via prototype devices, coatings and materials. Based on the encouraging results of recent experimental work, we believe that mathematically analysing drug release from OIs would very likely be a fruitful endeavour. Such an approach has the potential of accelerating the design of the enhanced drug-releasing OIs of the future.

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